

## CURRENT TOPIC

## The new antiepileptic drugs

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Seventy per cent of all children with epilepsy will have their seizures either well, or completely controlled by a single antiepileptic drug (AED). However, for the remaining 30%, seizure control may be much more difficult to achieve and may be associated either with unacceptable side effects or with having to resort to polytherapy (using two or more AEDs), or both. Although surgery is now becoming increasingly accepted as a realistic therapeutic option for some children with refractory seizures, it will not be suitable or appropriate for the majority. There is therefore a clear need for novel AEDs in treating paediatric epilepsy, which must be both effective (preferably with a broad spectrum of action against a wide range of seizure types) and safe.

While the advent and development of new AEDs must be welcomed, it is important to use the older, 'recommended' drugs (that is sodium valproate and carbamazepine) appropriately initially, particularly in view of the limited monotherapy efficacy and long term safety data of these new compounds; economic implications may also have to be considered, particularly in developing countries. The 'appropriate' use of an older drug includes using the correct AED for the specific epilepsy syndrome (for example sodium valproate and not carbamazepine for juvenile myoclonic epilepsy) and prescribing it to its maximally tolerated dose before abandoning it and substituting an alternative drug.

Another problem with the new AEDs is that there are very few randomised and controlled or comparative (or both) data in children, which reflects the difficulties in undertaking clinical trials in this age group.<sup>1</sup> Therefore any new AED is (and will continue to be for the foreseeable future) prescribed 'off-label' or outside the terms of the drug's product licence, in individual children, by their physician. It is also of interest that as far as the pharmaceutical industry is concerned (regarding one of the inclusion/exclusion criteria for drug trials), an 'adult' is defined as a person over the age of 12 years; clearly this is somewhat younger than the generally held belief that a person is a 'child' until the age of 16 years. Furthermore, close analysis reveals that very few 'adults' between 12 and 16 years of age are actually recruited into these drug trials.

As of February 1996, four new AEDs have been licenced for use in Great Britain; vigabatrin, lamotrigine, gabapentin, and most

recently, topiramate. In February 1995, lamotrigine received a monotherapy licence, but only for patients aged 12 years and above; it also has a licence as an 'add-on' treatment for children aged 2 years and older. Vigabatrin has a licence for add-on treatment only in children based on body weight, while gabapentin and topiramate currently only have licences for add-on treatment of partial seizures that are not satisfactorily controlled by other drugs in children aged 12 years and above. Paediatric data on topiramate are very limited and therefore this paper will focus on vigabatrin, lamotrigine, and gabapentin. (A comprehensive data sheet on each drug may be found in the ABPI data sheet compendium 1995-6, Datapharm Publications Ltd, London.)

### Vigabatrin

Vigabatrin, licensed for use as an add-on drug in 1989, was the first of the new antiepileptic drugs.<sup>2-3</sup> It was designed specifically as an irreversible inhibitor of  $\gamma$ -aminobutyric acid (GABA-aminotransaminase), inducing a dose dependent increase in the extracellular content of this potent inhibitory neurotransmitter, thereby theoretically increasing seizure suppression. Vigabatrin appears to be particularly useful in partial seizures with or without secondary generalisation; most studies suggest that between 45% and 80% of patients demonstrate a greater than 50% reduction in seizures,<sup>4-9</sup> with between 8 and 10% of children becoming seizure free. The interpretation of the results of the use of vigabatrin in generalised seizures in epilepsies has been more difficult.<sup>10</sup> Some generalised epilepsy syndromes (specifically the Lennox-Gastaut syndrome) are characterised by multiple seizure types which are frequently not analysed individually in terms of drug response.<sup>11-13</sup> The non-progressive myoclonic seizures which characterise some of the idiopathic (primary) generalised epilepsies (including juvenile myoclonic epilepsy) and the progressive myoclonic epilepsies tend to be exacerbated with between 25% and 50% of patients experiencing an increase in seizure frequency.<sup>7</sup> By contrast, vigabatrin is emerging as an effective drug in the treatment of infantile spasms (West's syndrome), a somewhat surprising observation as infantile spasms are currently classified as a type of myoclonic seizure. An initial study focused on 70 children with refractory or drug resistant spasms<sup>14</sup>; when vigabatrin was added

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to these patients' other AEDs, the spasms resolved in 29 (43%) and another 46 (86%) showed a greater than 50% reduction in spasm frequency. The most dramatic response was seen in tuberous sclerosis with 10 of 14 children with this disorder becoming spasm free; 36% of 36 children with cryptogenic (idiopathic) spasms also experienced complete spasm suppression. Subsequently, eight of these 70 children (11%) remained spasm free on vigabatrin monotherapy; unfortunately a number of these patients subsequently developed partial, and 'other' myoclonic seizures.

In view of these preliminary data, attention understandably focused on using vigabatrin as the initial drug of choice<sup>15-16</sup> instead of the previously 'recommended' treatments (adrenocorticotrophic hormone (ACTH) and prednisolone). A number of open studies have demonstrated that between 65 and 75% of children become spasm free with vigabatrin monotherapy irrespective of aetiology (symptomatic, cryptogenic, or idiopathic), with again, patients with tuberous sclerosis showing the best response.<sup>15-18</sup> A recent European retrospective study reported 68% of 192 patients showing an initial spasm suppression, although this number fell to 50% after a mean follow up period of nine months.<sup>19</sup> A recent survey among paediatric neurologists in the UK and Ireland indicated that over 75% would now use vigabatrin as the initial drug in treating infantile spasms of symptomatic origin and almost 50% would use it irrespective of aetiology.<sup>20</sup> In the author's opinion vigabatrin has been and will remain, the initial preferred treatment of infantile spasms; this opinion is shared by some, although not all, European countries.<sup>17-21</sup> Importantly, and at least in West's syndrome, the drug appears to work rapidly, usually within five to six days of its introduction; if spasms fail to respond (either partially or completely) after seven days, then alternative antiepileptic medication can then be introduced. However, there are still some outstanding questions regarding the long term effects of this drug and how soon after control of the spasms the drug can be discontinued; evidence is now accumulating that the drug can be successfully withdrawn after a number of months, without a corresponding relapse in either spasms or the development of new seizure types; clearly, this requires further evaluation.

Vigabatrin also appears to have a relatively impressive safety profile,<sup>3</sup> which in part reflects the fact that this drug is not metabolised by the liver and is eliminated virtually unchanged (70%) via the kidneys; the dose may therefore have to be reduced in patients with significant renal impairment. Allergic skin reactions are extremely rare (never described in children) and no blood dyscrasias have been reported. Transient sedation and dizziness are the most commonly described acute side effects, usually occurring only as the drug is introduced. Increased appetite (and consequent weight gain) have been reported in up to 15% of adult patients but this would appear to be considerably less prevalent in children and not as com-

mon as with sodium valproate; however, this latter observation may simply reflect the fact that vigabatrin is less frequently prescribed than sodium valproate. The most commonly reported side effects have been on behaviour and emotion, manifest by 'agitation', 'hyperkinesia', or altered muscle tone; psychosis has been reported rarely, although this appears to be more of an issue in adults. The incidence of these neuropsychiatric side effects has varied from 2<sup>8</sup>–25%.<sup>7</sup> One of the difficulties is that most of the children studied have already had pre-existing learning difficulties or behaviour problems, or both; it may therefore be difficult to differentiate between a genuine adverse event and a cyclical though still abnormal behaviour, in this particular population. What behavioural effects do occur appear to be transient and dose related particularly with how rapidly the drug is introduced and increased.<sup>7-8</sup> Perhaps surprisingly, significant behavioural abnormalities appear to be uncommon in children with infantile spasms where vigabatrin is introduced and increased relatively rapidly. Acute psychosis seems to be more of a problem in the adult population where its pathogenesis is not entirely clear<sup>22-24</sup>; in some situations it may be due to a phenomenon known as 'forced normalisation', where patients' behaviour becomes markedly disturbed after the rapid and complete control of frequent seizures that may have been occurring for many years. Limited adult data suggest that vigabatrin has no significant adverse effect on memory or cognitive function.<sup>25</sup>

One of the main concerns about vigabatrin has focused on its reported neuropathological effects. However, the reversible microvacuolation that has been observed in the myelin (particularly in the cerebellum) of rats and dogs has not been seen in primates or humans either on magnetic resonance imaging, neurophysiology (visual and somatosensory evoked responses), or in detailed histological analysis of postmortem or surgically resected tissue from patients (including children as young as 20 months) treated with this drug.<sup>26-29</sup> Although these preliminary observations are encouraging, further neuropathological data are required to evaluate the long term use of vigabatrin in the immature, developing brains of infants and young children (particularly those treated for infantile spasms).

There are very few data on the teratogenic potential of vigabatrin; cleft palate has been observed in white rabbits and, thus far, no obvious drug related malformations/deformations have been seen in a number of fetuses born to women receiving vigabatrin throughout pregnancy. There is no information on the safety of vigabatrin while breast feeding.

There is no 'recommended' dosing regimen for the drug, other than exists in its data sheet. From the author's personal experience, and irrespective of seizure type (including infantile spasms), a suggested starting dose is 40–50 mg/kg/day (given as a twice, or much less commonly, once daily dose), increasing to 80–100 mg/kg/day over either three days (when treat-

ing infantile spasms) or over two weeks when treating other seizure types. Occasionally, and only if suggested by an initial good clinical response, could the dose be increased to 120–150 mg/kg/day, again, irrespective of seizure type. Further increases are probably unnecessary as limited data suggest that there is no obvious dose response relationship.<sup>9</sup>

Vigabatrin shows no clinically significant interaction with any other drug, including the oral contraceptive and other AEDs.<sup>3</sup> The plasma concentration of phenytoin may fall by up to 30% (the mechanism of which is unclear), but this does not appear to have any adverse effect on seizure control. Finally, there is no correlation between plasma concentrations of vigabatrin and its clinical efficacy, due to its pharmacokinetic properties; this therefore obviates the need for blood level monitoring, except if establishing major non-compliance. The drug is available as a 500 mg tablet or as a white powder (containing 500 mg per sachet which dissolves completely in most liquids, yielding a colourless, odourless, and almost tasteless solution). All of these issues (no significant drug interaction; no clear dose response relationship; almost clinically irrelevant blood level monitoring; and a paediatric friendly formulation) are important factors for the practical use of this drug and in many ways render it the most 'ideal' of the new AEDs.

### Lamotrigine

Lamotrigine is the second of the newer AEDs licenced in 1992, again, initially as an add-on drug for partial seizures not responding satisfactorily to other drugs. It has subsequently been the first to be granted a monotherapy licence, but only for children aged 12 years and above; the licence has not (as yet) been extended for younger children, because of inadequate efficacy and safety data. The precise mechanism of action of lamotrigine remains unclear, although it may act by inhibiting the release of excitatory amino acids (for example glutamate and aspartate) through voltage dependent sodium channels.<sup>30</sup> Although the drug is structurally related to antifolate drugs, lamotrigine has only weak activity against folate in animals thereby refuting an early hypothesis that its antiepileptic activity might involve the metabolism of folic acid. Double blind, placebo control studies undertaken throughout the world demonstrated a mean reduction (that is 50% or greater reduction) of all seizure types in between 17 and 59% of all adult patients studied.<sup>31 32</sup> Pooled data from many sources (all open, add-on studies involving 572 adult patients) also showed that many different seizure types appear to respond to lamotrigine, and not just partial seizures<sup>33</sup>; specifically 64% of patients with atypical absences, 50% of patients with tonic-clonic seizures, and 50% of patients with atonic seizures experienced a greater than 50% reduction in seizure frequency.<sup>31 32</sup> Similar results have been reported in children; from a pooled paediatric population of 285 children (in open, add-on studies), 34% of patients achieved a greater than 50% reduction in all

seizures.<sup>34</sup> Furthermore, 50%, 38%, and 31% of patients with atypical absences, atonic, and myoclonic seizures respectively also demonstrated a greater than 50% reduction in seizure frequency with some children becoming seizure free.<sup>34</sup> Other studies have also indicated that myoclonic and atypical absences show a good response to this drug.<sup>35–37</sup> These data are encouraging because it is often the generalised, rather than partial seizures that are the more frequent and intractable seizure types of early and mid-childhood. Consequently, the drug developed a reputation for a broader spectrum of anticonvulsant action and, not surprisingly, this has contributed to lamotrigine being the first of the new AEDs to be granted a monotherapy licence, and to be awarded the 1995 UK Prix Galien (for the 'most innovative medicine'). Lamotrigine is now becoming regarded as the drug of first choice for children with the Lennox-Gastaut syndrome, in view of its broad spectrum of action (as this syndrome is characterised by multiple, and generalised seizure types) and its relatively good safety profile (see below). Most recently, the drug has shown some effect in the treatment of intractable infantile spasms which have not responded to other AEDs including vigabatrin.<sup>38</sup>

Preliminary data suggested that lamotrigine may also have a positive psychotropic (attention and mood enhancing) effect in some children with learning and behaviour difficulties, irrespective of seizure control<sup>35 37 39 40</sup>; this clearly requires further study. Finally, there is also evidence that lamotrigine may have a 'beneficial effect' on the electroencephalogram (EEG)<sup>41</sup> in suppressing photically induced photosensitivity and, importantly, interictal (that is subclinical) epileptiform (spike) activity.<sup>42 43</sup>

Evidence is also accumulating (predominantly anecdotal) that there is an effective synergy between sodium valproate and lamotrigine for generalised tonic-clonic, atonic, and myoclonic<sup>44</sup> seizures, and ethosuximide and lamotrigine for typical absences<sup>45</sup> (either childhood or juvenile onset).

Lamotrigine also appears to have relatively few side effects. The most commonly reported adverse effects reported in at least 10% of all children evaluated in all paediatric studies, included drowsiness, skin rash, and vomiting.<sup>34 46</sup> Other less commonly reported side effects have included rhinitis, ataxia, 'hyperkinesia', and headache.<sup>34</sup> In clinical practice, the skin rash is potentially the most serious, both in terms of the acute systemic disturbance (pyrexia, vomiting, and rarely the Stevens-Johnson syndrome), which may accompany the development of the rash, and the fact that the patient may never be able to receive lamotrigine in the future because of the sensitisation to the drug. The rash usually develops in the first 10–14 days of treatment, is diffuse, maculopapular (resembling measles), and is often pruritic. It is important that the rash is confirmed as being due to the drug (and not to a viral infection or other allergy) and then stopped immediately. This may have to be undertaken in hospital depending on the over-

all clinical condition of the child and the fact that abrupt drug discontinuation may, in certain situations, exacerbate seizure frequency and even precipitate convulsive status epilepticus. However, in practice this is unlikely to occur as the child will have only been receiving lamotrigine for a relatively short period. It is now clear that the incidence of the rash is directly related to the starting dose of the drug and the rate at which the dose is increased, particularly if the patient is already receiving sodium valproate. In the author's experience of introducing lamotrigine slowly (either as monotherapy or polytherapy with sodium valproate) to over 50 children over the past three years, skin rash has not been seen. Finally, lamotrigine has been successfully reintroduced in a few children who had developed a rash with the initial use of the drug (personal data).

Because lamotrigine is a weak inhibitor of dihydrofolate reductase, there is a theoretical risk of human fetal malformations if the mother is treated with the drug during pregnancy. However, toxicology data from both animal studies and over 80 completed pregnancies of women treated with lamotrigine have not shown any obvious drug related teratogenicity in these fetuses. There is no information on the concentration of lamotrigine in breast milk or its effect on breast feeding and the nursing infant.

The 'recommended' dosing regimen clearly reflects the concern over the skin rash; the drug's data sheet recommends two separate regimens, one for children also receiving sodium valproate and another for those who are receiving other AEDs or (for those children who are 12 years and over), who are to be prescribed lamotrigine as monotherapy. In addition, the initial 'target' maintenance dose is different in the two groups. It is also recommended that each incremental increase in dose should only be made every two weeks. In the author's experience this is somewhat complicated and to simplify the regimen, begins with 0.3–0.4 mg/kg/day (irrespective of whether the child is already receiving sodium valproate) with further increases every two weeks, up to an initial 'target' maintenance dose of *either* 4–6 mg/kg/day (for those also receiving sodium valproate) *or* 8–12 mg/kg/day (for those not receiving sodium valproate). The drug is usually given once a day for the first two to four weeks, and thereafter twice daily. Obviously, it will take some weeks to achieve the 'target' maintenance dose, whichever regimen is used. The family should therefore be forewarned of this and the fact that any benefit on seizure control may take up to 4–6 weeks (or longer). This slow introduction (which is often paralleled by families' and clinicians' frustration) is almost certainly justified because of the drug's emerging impressive antiepileptic and safety profile. The one seizure type/epilepsy syndrome where this may not be so readily acceptable is in infantile spasms/West's syndrome where 'early' control is considered important, although it is likely that the underlying cause, rather than the speed

with which the spasms are controlled, ultimately determines both the short and long term prognosis in this syndrome. Finally, and again because of the fact that clinical experience with this drug is still growing, the maximum or ceiling dose of lamotrigine has yet to be determined; anecdotal experience (including the author's) suggests that doses up to 18–20 mg/kg/day (in patients not receiving sodium valproate) may still result in good (if not complete) seizure control, without the development of any significant adverse effects.

The single most important drug interaction is with sodium valproate, which delays the hepatic metabolism of lamotrigine, thereby increasing its half life from approximately 24 to 45–60 hours. When lamotrigine is taken in conjunction with liver enzyme inducing drugs (for example carbamazepine and phenytoin) the half life is shortened from 24 to 14 hours. Interaction between lamotrigine and carbamazepine has also been reported,<sup>47</sup> producing a 45% increase in the concentration of the 10,11-epoxide metabolite of carbamazepine with some resulting clinical toxicity (dizziness or ataxia, nausea, and diplopia). Lamotrigine is currently available in tablet form (25, 50, 100, and 200 mg) and also as a dispersible or chewable tablet (5, 25, and 100 mg).

### Gabapentin

Gabapentin was licensed for use in adults and children aged 12 and over as an add-on treatment for 'partial seizures with/without secondary generalisation in patients who have not achieved satisfactory control with, or who are intolerant to, standard anticonvulsants used alone or in combination' (entry in the data sheet compendium 1995–6). Although similar in structure to GABA, it does not appear to act pharmacologically as a GABA mimetic. Its mechanism of action remains unclear, although recent data suggest that it may be acting on a novel receptor binding site involving a calcium channel. Efficacy and safety data on the use of gabapentin in children are very limited; a UK and international double blind, placebo controlled study of approximately 250 children aged 4 to 12 years of age, with refractory partial seizures is on-going with preliminary results expected in 1997. Gabapentin (as monotherapy) is also currently being evaluated in the USA in the treatment of benign partial epilepsy with centrotemporal (rolandic) spikes/sharp waves (BREC). In adults, the drug is effective in partial and secondarily generalised seizures<sup>48, 49</sup>; between 20 and 28% of adults showed a greater than 50% reduction in seizure frequency, and there was a clear and linear dose response relationship. As yet, there is little information on primary generalised seizures/epilepsy syndromes. Two double blind, placebo controlled studies in the USA failed to show any statistically significant effect of gabapentin on either the seizure frequency or EEGs of children with typical absence epilepsy.<sup>50</sup>

Adverse events appear to be both mild and infrequent, which may again reflect the fact

that gabapentin like vigabatrin is not metabolised in the liver and is eliminated unchanged via the kidneys. No allergic or idiosyncratic reactions (on the skin or haemopoietic system) have been reported. As with any AED, drowsiness, dizziness, ataxia and fatigue may occur, but these are usually transient and do not necessitate a reduction in dosage. Long term use is rarely complicated by neuropsychiatric adverse effects including personality changes, 'agitation', depersonalisation, and frank psychosis.<sup>51</sup> Recently, similar behavioural disturbances have been reported in children<sup>52-54</sup>; however, this has not (thus far) been reflected in over 60 children treated in the open phase of the UK/international paediatric study cited above. Toxicology data have shown an increase in the incidence of low grade malignant tumours of the acinar cells of the pancreas in the males of one particular strain of rat (Wistar) at very high doses of between 250 and 2000 mg/kg/day.

No obvious drug related teratogenic effects have been described thus far in animals or a number of fetuses whose mothers have taken gabapentin throughout their pregnancy. There is no information on whether gabapentin is excreted in human milk and its effect on breast feeding and the nursing infant.

Gabapentin does not appear to interact with any other drug, including the oral contraceptive and other AEDs. Co-medication with cimetidine did result in a 12% decrease in the renal clearance of gabapentin but this is unlikely to be of any clinical significance. The elimination half life of gabapentin ranges from 5-7 hours.<sup>55</sup> The time of peak anticonvulsant action of gabapentin is delayed approximately two hours after intravenous administration, beyond the time of peak drug concentration in either the blood plasma or brain extracellular space. Whatever the explanation for this, it would imply a limited clinical role for monitoring plasma concentrations of gabapentin, other than in possibly detecting major non-compliance.

Unfortunately (for paediatric use) the drug is only currently available as an oral capsule in doses of 100, 300, and 400 mg. The contents of the capsule are extremely bitter and this therefore usually militates against the capsule being opened and disguising the taste of the powder with a favourite juice or food. In the author's experience concentrated blackcurrant juice (Ribena) provides the most effective (but not always successful) 'mask' for this bitter taste. Another disadvantage is that gabapentin must be given three times a day in view of its short half life; this frequently necessitates giving the drug during school hours which may be difficult (if not unacceptable) in certain situations. There is some evidence (personal data from adult neurologists and from the author's own experience) that it may still be as effective when given as a twice daily dosing regimen, although it must be emphasised that this is currently contrary to the drug's data sheet.

For obvious reasons, there are as yet no 'recommended' starting or maintenance doses for

children (under the age of 12 years). However, for adults (and therefore teenagers) the recommended starting dose is 400 mg a day increasing over 3-7 days to an initial and 'target' maintenance dose of 400 or 600 mg three times a day; doses of up to 900 or 1000 mg three times a day have occasionally been prescribed without causing any significant adverse events. For younger children, the author's preference is to begin with approximately 10-15 mg/kg/day increasing every seven days to an initial 'target' maintenance dose of approximately 35-45 mg/kg/day. Providing there has been some initial response, the dose can be increased up to 60 mg/kg/day without the development of any significant adverse effects. The maximum or ceiling dose of gabapentin has yet to be determined—for both adults and children.<sup>56</sup>

In many ways, gabapentin also fulfills some of the criteria for an ideal AED: it is not metabolised, does not bind to plasma proteins, does not induce or inhibit hepatic enzymes, shows no significant drug interactions, and does not require plasma level monitoring. However, it does require a thrice daily dosing regimen, has an obvious linear dose response relationship and, as yet, there is no paediatric friendly formulation.

### Felbamate

Up until early 1995 felbamate was available on a compassionate named patient basis. Preliminary reports from the USA had suggested that it was effective for partial and secondarily generalised seizures in adults<sup>57, 58</sup> and generalised seizures associated with the Lennox-Gastaut syndrome in children<sup>59, 60</sup>; however, no child was rendered seizure free in this latter study. Unfortunately, a disproportionately large number of patients developed aplastic anaemia (21 as of August 1994, including two children), some with a fatal outcome.<sup>60, 61</sup> A severe (also presumed idiosyncratic) hepatitis was subsequently reported. Additional difficulties with using felbamate included a three or four times a day dosing regimen, major interactions with carbamazepine, phenytoin, and sodium valproate and other significant side effects, including insomnia, anorexia, and diarrhoea. In view of these difficulties/side effects felbamate is no longer currently available in the UK but continues to be prescribed in the USA, although, not surprisingly with some patient/parental anxieties.<sup>62-64</sup>

Within the UK, and before its withdrawal, the drug certainly had some advocates among both families and clinicians; however, it is uncertain whether felbamate will ever re-emerge in this country in view of its potentially sinister safety profile and the advent of newer (and safer) AEDs.

### Conclusion

Of the three newly licensed AEDs, vigabatrin is arguably the easiest to use and is emerging as the drug of first choice in infantile spasms and (frequently) the drug of second choice in partial seizures with or without secondary gen-

eralisation. Lamotrigine would appear to have the broadest spectrum of action and, excluding the skin rash issue, has an impressive safety profile; it is becoming regarded as the alternative to/replacement for sodium valproate. Gabapentin's full antiepileptic potential has yet to be realised but it does appear to be particularly safe and free of interactions with any other drugs, and it should certainly be considered before the use of the older AEDs (that is phenytoin and phenobarbitone) in the treatment of partial and secondarily generalised seizures.<sup>65</sup>

Further data are clearly required particularly in children,<sup>66</sup> predominantly using monotherapy comparative studies. Placebo controlled studies simply show (hopefully) that the drug is effective and safe and therefore facilitates the granting of a product licence; comparative studies (against the more established first line drugs, namely sodium valproate and carbamazepine) will demonstrate whether these newer drugs are more effective and safer, and therefore, whether they should replace sodium valproate and carbamazepine as the drugs of first choice in the treatment of the paediatric epilepsies. Thus far only two such studies have been undertaken with vigabatrin<sup>67</sup> and lamotrigine<sup>68</sup> (both versus carbamazepine, in adult patients). It will also be important to monitor the tolerability (that is the sustained effect) of the new AEDs and also the long term effects on learning and behaviour. In the older child lamotrigine is being prescribed more frequently as monotherapy; some clinicians are already recommending that for women of child bearing age (which obviously may include a number of teenagers), presenting with a newly diagnosed primary generalised epilepsy, lamotrigine, rather than sodium valproate should be the drug of choice based on the fact that the latter drug is associated with a 10-fold increased risk of causing neural tube defects and that lamotrigine *appears* to be at least as efficacious as sodium valproate, and perhaps less teratogenic. Such a recommendation is considered to be somewhat premature by other clinicians (including the author), in view of the still limited efficacy and safety data on the use of lamotrigine in pregnancy.

Finally, the advent of the new AEDs has paradoxically and perhaps, in contrast to what was expected, contributed to a degree of therapeutic confusion—which drug should be prescribed first and which is the next most appropriate drug, and in what dose. At least five other novel AEDs are currently being evaluated: topiramate,<sup>69,70</sup> tiagabine,<sup>71</sup> zonisamide, remacemide, and stiripentol. This is likely to further complicate the treatment and overall management of children with epilepsy, particularly among those clinicians who have neither a specific interest nor an expertise in epilepsy.

### Addendum

From March of 1996 a monotherapy licence has been granted for the use of vigabatrin in the management of children with infantile spasms (West's syndrome) in the UK.

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